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CONTRACTING ORGANIZATION: The University of Adelaide
Osaka, Japan

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14. ABSTRACT We are second-year into the three-years of our research program into the immunogenetics and drug exposure factors that contribute to chronic pain following spinal cord injury. Administrative advances made in the second year for Study 1 Site 2 (NSW) include submitting a full NEAF after the review of the initial Low – Negligible Risk (LNR) admission was considered to not contain enough information for full review by Human Ethics Research Committee in NSW. Recruitment for Study 1 Site 1 (Royal Adelaide Hospital) includes 173 study invitations letters sent out, 37 consent forms returned & sample/questionnaire mail-outs, 26 buccal samples collected & DNA genotyping completed, 26 participant medical history reports entered into database. We anticipate a quick response from HERC-NSW regarding the NEAF to then begin recruitment from Site 2 in the next 1-2 months. Study 2: We have initiated study 2 recruitment, screening and testing and data collection in underway.					
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INTRODUCTION

Spinal cord injury results in significant trauma and inflammation originating at the site of injury as well as from various systemic anatomical compartments. This inflammatory event provides both beneficial activation of repair and clearance systems, but also creates long-term detrimental consequences such as chronic pain. Chronic pain develops after spinal cord injury in more than 65% of the clinical population¹. However, the reasons as why some patients develop chronic pain and others do not remains unknown. Chronic neuropathic pain elicits a number of changes in the activity, properties and transmitter content of pain-pathway neurons². This central sensitization to nociceptive stimuli culminates in profound debilitating pain that serves no adaptive purpose for the sufferer. It is now established that spinal inflammatory events resulting from numerous stimuli initiate and maintain chronic neuropathic pain conditions³ and may result from a dysregulation of the spinal immunocompetent cells, glia, and their up regulation of pronociceptive (pain) systems. A key event in the initiation of this inflammatory response is the activation of the innate immune system pattern recognition receptor, Toll Like Receptor 4 (TLR4)^{4,5}. TLR4 is able to detect the presence of endogenous danger molecular patterns resulting in the activation of an inflammatory cascade that results in the expression and release of a myriad of inflammatory signals such as proinflammatory cytokines, chemokines, prostaglandins, reactive oxygen species and nitric oxide. Importantly, these same proinflammatory molecular signals also elicit a pronociceptive, or painful, response that contributes indelibly to the chronic pain state⁵. The prototypic opioid, morphine, is capable of TLR4-mediated proinflammation⁶⁻⁸. As such, exposure to morphine at the time of injury may result in exacerbated proinflammation and hence produce long-term consequences for the pain susceptibility of the individual. In addition, the immune genes that encode these key inflammatory mediators are highly polymorphic. Hence, an individual may have a genetic predisposition to over respond in a proinflammatory fashion to the spinal cord injury and/or to experience inflammation in response to opioid exposure. Critically, this genetic variability may significantly impact the long-term health and quality of life of the individual. Thus both genetics and drug exposure at the time of injury may be contributing factors individually and/or interactively that may lead some individuals to develop chronic pain following injury or may protect others from developing pain pathology. Hence, this project will investigate the impact of both pharmacological agents and genetic variability on the occurrence of chronic pain following spinal cord injury.

BODY

The research management team (Dr Hutchinson, Dr Collier & Dr Clarke) have continued to meet and communicate regularly during year 2 of the research project to ensure administrative progress. Communication between the research management team and the clinical trials staff has also increased to ensure timely and efficient conduct of study 2.

Our professional research team includes Ms Vicky Staikopoulos, Ms Francesca Alvaro and Ms Kathy Heyman. Vicky is our highly experienced technical research assistant (working 3 days a week) who continues to coordinate the lab side of the team to prepare our mail-outs, process DNA samples and receive data back from our analysis centre. Kathy and Francesca form the hands on part of our clinical team who are

engaged at the Hospital and the Rehabilitation Centre. They liaise with Dr Marshall and Dr Clarke to coordinate the subject recruitment and consenting. Kathy is a registered nurse and Francesca has many years clinical trials experience. Kathy and Francesca job share approximately a 3-4 day load.

This arrangement is working very well to ensure a balance of strict patient information confidentiality at the hospital side and timely outcomes at the lab side. All staff and investigators have completed NIH Human Research training and their details and credentials have been passed onto the Human Research Protection Office.

STUDY 1

Human research ethics for Study 1 Site 1 has been approved by the research ethics committee at the Royal Adelaide Hospital (Site 1: approval no. 111008) and approved by the Human Research Protection Office (16986.1). Study 1 Site 2 ethics has been re-submitted and is under review for patient recruitment in New South Wales. The clinical team at Site 1 (Hampstead Rehabilitation Centre, Royal Adelaide Hospital) has identified 791 patients in their database who fulfill the inclusion criteria for Study 1. They have been processing 20-30 recruitment and questionnaire/sample mail-outs per week. To date, 173 study invitation letters have been sent out; 37 people have returned signed consent forms and have had Buccal swab/Questionnaire packs sent to them. This recruitment rate has been of significant concern as it is not in line with this research groups past experiences with this population. We are continuing to make follow-up phone calls to those participants who have been sent study invitations letters but have not responded, in the anticipation of increasing the participation rate of those initially contacted. The aim is to have begun Site 2 (NSW) recruitment in Oct 2013, following an expedited review of the Site 2 Human Research Ethics Application submitted. Significant delays in processing the Site 2 ethics were expectantly encountered during 2013 due to NSW ethics office closures and moves. However, these issues have now been overcome and approval is pending.

DNA genotyping has begun from Site 1 participants that have returned samples and this data has been entered along with the participant's medical history.

Parallel these efforts we are nearing the completion of the processing of DNA samples from the healthy control reference sample population. Additionally, our clinical team is reviewing the clinical records of the recruited and consented patients from Study 1 Site 1 and this data collection process has begun. We have engaged with local spinal cord injury support networks to also improve patient recruitment. Through ongoing engagement with the local support groups, opening of site 2 recruitment and holding public information sessions we believe Study 1 recruitment goals will be met.

STUDY 2

Study 2 institutional Ethics approval has been gained (Approval no. 111035) and Human Research Protection Office (HRPO) approval has been granted (16986.2). Study 2 has begun recruiting participants and data from the first 2 participants has been successfully collected.

The processing data pipeline has been constructed and is being employed in all data collection to date.

KEY RESEARCH ACCOMPLISHMENTS

Human research ethics approval granted for Study 1.1 (SA: RAH)
HRPO approval gained for Study 1.1 (SA: RAH)
Subject recruitment commenced for Study 1.1 (SA: RAH)
Human research ethics application re-submitted for Study 1.2 (NSW: RNS)
Human research ethics approval granted for Study 2
HRPO approval gained for Study 2
Subject recruitment commenced for Study 2

REPORTABLE OUTCOMES

Approval for site 2 (NSW) of Study 1 is still ongoing after the initial Low-Negligible Risk application submitted in 12th July 2012 was rejected with comments in a letter dated 14th August 2013 stating that the project was not considered LNR and a full NEAF application would be required. This full NEAF application has been submitted (Oct 2013) to the Northern Sydney Local Health District (NSLHD) HREC committee for speedy review.

CONCLUSION

(CONCLUSION: *Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.)*

Since the awarding of this grant, publications of additional parallel basic mechanistic research by our group and others around the world continues to support the core hypothesis underlying this research program, exposure to drugs, such as opioid analgesics at the time of spinal cord injury may result in profound alternations in the proinflammatory environment within the central nervous system that may produce long-term consequences for the pain susceptibility of the individual.

Thus, genetic polymorphisms in the immune genes responsible for this immune response may have a genetic predisposition to over respond in a proinflammatory fashion to the spinal cord injury and/or to experience inflammation in response to opioid exposure. Critically, this genetic variability may significantly impact the long-term health and quality of life of the individual. Thus both genetics and drug exposure at the time of injury may be contributing factors individually and/or interactively that lead some individuals to develop chronic pain following injury or may protect others from developing a pain pathology. The data collected from the 2 studies to be carried out here will provide critical clinical evidence to support these hypotheses

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APPENDICES

1. Approval letter from the RAH Human Research Ethics Committee for Study 2
2. Approval email from the HRPO for Study 2



8 October 2012

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Research Ethics Committee

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Email: Heather.O'Dea@health.sa.gov.au

Dear Dr Hutchinson

Re: "Immune genetic studies of opioid use and experimental pain sensitivity following spinal cord injury."

RAH PROTOCOL NO: 111035.

I am pleased to advise that Research Ethics Committee APPROVAL is granted to the above project on the above date. The following have been reviewed and approved:

- **Protocol SCL002, Version 3 (24 September 2012)**
- **Participant Information Sheet & Informed Consent Form – Spinal Cord Injury, Version 3 (24 September 2012)**
- **Participant Information Sheet & Informed Consent Form – Chronic Pain, Version 3 (24 September 2012)**
- **Participant Information Sheet & Informed Consent Form – Healthy Participants, Version 3 (24 September 2012)**
- **Spinal Cord Injury Patient Study Invitation Letter (24 September 2012)**
- **Chronic Pain Patient Study Invitation Letter (24 September 2012)**
- **Healthy Control Study Invitation Letter (24 September 2012)**
- **Spinal Cord Injury Patient Questionnaire (24 September 2012)**
- **Chronic Pain Patient Questionnaire (24 September 2012)**
- **Treatment Algorithm for Autonomic Dysreflexia (Hypertensive Crisis) in Spinal Cord Injury (10 April 2006)**
- **Treatment Algorithm for Autonomic Dysreflexia (Hypertensive Crisis) in Spinal Cord Injury (2010)**

Please quote the RAH Protocol Number allocated to your study on all future correspondence. Research Ethics Committee deliberations are guided by the NHMRC National Statement on Ethical Conduct in Human Research 2007.

GENERAL TERMS AND CONDITIONS OF ETHICAL APPROVAL:

- For all clinical trials, the study must be registered in a publicly accessible trials registry prior to enrolment of the first participant.
- Adequate record-keeping is important. If the project involves signed consent, you should retain the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them in the future if necessary. The duration of record retention for all clinical research data is 15 years.
- You must notify the Research Ethics Committee of any events which might warrant review of the approval or which warrant new information being presented to research participants, including:
 - (a) serious or unexpected adverse events which warrant protocol change or notification to research participants,
 - (b) changes to the protocol,
 - (c) premature termination of the study,
 - (d) a study completion report within 3 months of the project completion.
- The Committee must be notified within 72 hours of any serious adverse event occurring at this site.
- Approval is **ongoing**, subject to satisfactory annual review. Investigators are responsible for providing an annual review to the RAH REC Executive Officer each anniversary of the final approval date using the Annual Review Form available at: <http://www.rah.sa.gov.au/rec/index.php> The REC must be advised with a report or in writing when this study is complete so that the file can be closed.

Yours sincerely,

Dr A Thornton
CHAIRMAN
RESEARCH ETHICS COMMITTEE

"Brosch, Laura R Dr CIV USA MEDCOM USAMRMC" <Laura.Brosch@us.army.mil>

1 March 2013 5:01 AM

Resent-From: <mark.hutchinson@adelaide.edu.au>

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A-16986.2, HRPO Approval Memorandum (Proposal Log Number SC100231, Award Number W81XWH-11-1-0806) (UNCLASSIFIED)

Classification: UNCLASSIFIED

Caveats: NONE

SUBJECT: Initial Approval for the Protocol, "Immune Genetic Studies of Opioid Use and Experimental Pain Sensitivity Following Spinal Cord Injury," Submitted by Mark R. Hutchinson, PhD, University of Adelaide, Adelaide, Australia, in Support of the Proposal, "Chronic Pain Following Spinal Cord Injury: The Role of Immunogenetics and Time of Injury Pain Treatment," Proposal Log Number SC100231, Award Number W81XWH-11-1-0806, HRPO Log Number A-16986.2

1. The subject protocol (version 4/dated 12 February 2013) was approved by the University of Adelaide Human Research Ethics Committee (HREC) on 20 February 2013. This protocol was reviewed by the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) and found to comply with applicable DOD, US Army, and USAMRMC human subjects protection requirements.
2. This greater than minimal risk study is approved for the enrollment of 120 subjects (60 patients with spinal cord injury, 30 patients with chronic pain, and 30 healthy controls).
3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRMC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.
4. Please note that a Research Monitor (RM) is required to be involved in DOD-supported research studies that are determined to pose more than minimal risk to subjects (DOD Instruction 3216.02, Nov 2011). If the duties of the RM (referred to a Medical Monitor in your protocol) could require disclosure of subjects' Protected Health Information outside a covered entity (i.e., the RM is not an agent of the covered entity), your institution may require the identity and location of the RM to be described in the study Health Information Portability and Accountability Act authorization.
5. Please note the following reporting obligations. Failure to comply could result in suspension of funding.
 - a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects. All other amendments must be submitted with the continuing review report.
 - b. All unanticipated problems involving risk to subjects or others must be promptly reported by phone (301-619-2165), by email (HRPO@amedd.army.mil<mailto:HRPO@amedd.army.mil>), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.
 - c. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the institutional review board, the institution, the sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.
 - d. A copy of the continuing review report and the re-approval notification by the University of Adelaide HREC must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the current approval by the University of Adelaide HREC expires on 8 October 2013. Please note that the HRPO also conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.
 - e. The final study report submitted to the University of Adelaide HREC, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.
 - f. The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this research; the issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any regulatory agencies including legal or medical actions; and any instances of serious or continuing noncompliance with the regulations or requirements must be reported immediately to the HRPO.
6. Please note: The USAMRMC ORP HRPO conducts random site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.
7. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.
8. The HRPO point of contact for this study is Melanie Frank, BSN, RN, Human Subjects Protection Scientist, at 301-619-6766 or Melanie.frank1@us.army.mil<mailto:Melanie.frank1@us.army.mil>.

LAURA R. BROSCH, PhD
Director, Office of Research Protections
Director, Human Research Protection Office
US Army Medical Research and Materiel Command

Note: The official copy of this memo is housed with the protocol file at the Office of Research Protections, Human Research Protections Office, 504 Scott Street, Fort Detrick, MD 21702. Signed copies will be provided upon request.

Classification: UNCLASSIFIED

Caveats: NONE